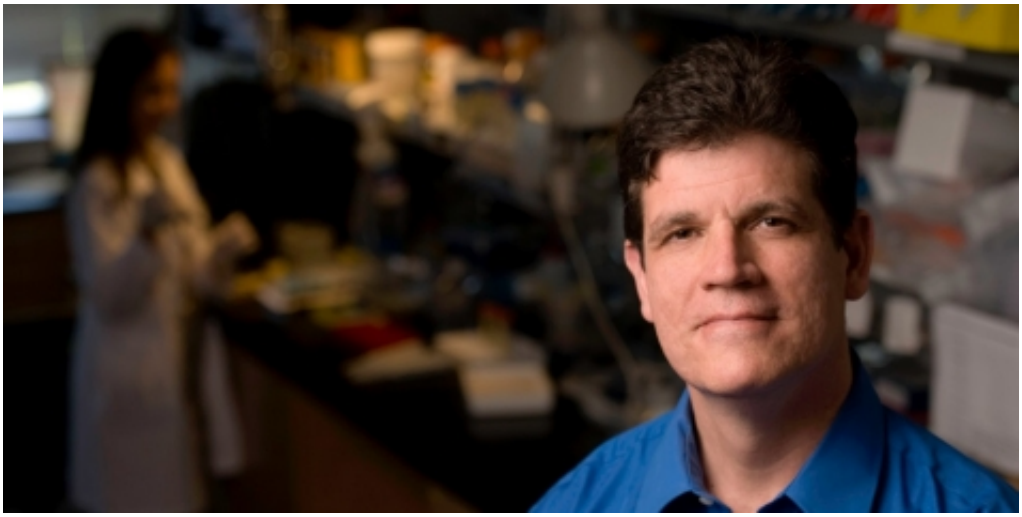
Blocking a metabolic pathway may shrink aggressive form of common kidney cancer

May 12 2015, by Krista Conger



Dean Felsher and his colleagues developed a mouse model that may help them find a way to treat kidney and other types of cancer. Credit: Steve Fisch

The first mouse model of an aggressive form of kidney cancer has identified an Achilles' heel in the disease that could lead to new treatment approaches in humans, according to a study by researchers at the School of Medicine.

Specifically, the cancer cells appear to rely primarily on the metabolism of an amino acid called glutamine for their energy. Blocking glutamine metabolism in mice caused their tumors to quickly shrink.

The tumor's reliance on glutamine is due to the effect of a cancer-associated gene called Myc. About 20 percent of people with kidney cancer have tumors that express abnormally high levels of Myc. But until now, the exact role the protein played in the condition was unknown.

"In the future, we hope to use this model to categorize different types of kidney cancer and identify those patients who might respond favorably to specific therapies," said Dean Felsher, MD, PhD, professor of medicine. "In the near term, we can test whether blocking glutamine metabolism is a viable approach for people with Myc-dependent liver cancer."

Felsher shares senior authorship of the study, which was published online May 11 in the *Proceedings of the National Academy of Sciences*, with Richard Zare, PhD, a professor of chemistry. Postdoctoral scholar Emelyn Shroff, PhD, is the lead author.

A new strain of mice

Renal cell adenocarcinoma is the most common type of kidney cancer in adults. It develops in the lining of small tubes in the kidney that transport waste from the blood to the urine. It can be difficult to diagnose, and people with advanced cases often have a poor prognosis.

The researchers genetically engineered a strain of mice to make either Myc or another cancer-associated protein called Ras in the proximal tubules of the kidney when a compound called doxycycline, which had been added to their drinking water, was removed from it. (Myc and Ras are not normally produced at high levels by these cells.) Ras-producing mice did not get cancer. But within just a few weeks, the mice that made Myc developed kidney cancers that mimicked an aggressive subset of human renal cell adenocarcinoma that originates in the kidney's collecting ducts. Adding doxycycline back to the animals' water caused

the tumors to shrink dramatically.

The researchers then turned to a new tissue analysis technique called desorption electrospray ionization mass-spectrometric imaging, or DESI-MSI, recently developed by postdoctoral scholar Livia Eberlin, PhD, in the Zare laboratory to compare cancerous and normal tissue.

DESI-MSI creates a highly detailed, two-dimensional map of the chemical composition of a tissue sample through a process that can be loosely compared to a specialized car wash. Samples are sprayed with a thin, high-powered stream of liquid droplets that dissolve their outer surface. The resulting back spray, which contains molecules from the surface of the sample, is collected and analyzed by mass spectrometry. By moving the sample around in a two-dimensional plane, it's possible to make a chemical map of the tissue.

Distinct chemical composition

The researchers found that the cancerous kidney tissue had a chemical composition distinct from that of healthy tissue. In particular, it had higher-than-normal levels of molecules generated as glutamine is metabolized. Blocking the activity of a protein called glutaminase, which is responsible for metabolizing glutamine, caused the animals' tumors to grow more slowly when doxycycline was removed from their drinking water.

Finally, the researchers showed that both Myc and glutaminase levels are also high in human samples of renal cell adenocarcinoma tumors, indicating that it may be useful to test whether blocking the glutamine pathway is a viable treatment for patients with the disease.

The researchers are now planning to create additional mouse models of other types of kidney cancer. "Using this new technique, we may now be

able to sort many kidney cancers into discrete types. We're also planning on using DESI-MSI to find new therapies for kidney but also liver cancers and lymphomas," Felsher said

Felsher emphasized that the study was only possible with the concerted effort of chemists in the Zare laboratory. "This was a true cross-disciplinary effort," Felsher said. "I am proud and excited about the outcome of this collaboration."

More information: MYC oncogene overexpression drives renal cell carcinoma in a mouse model through glutamine metabolism, www.pnas.org/cgi/doi/10.1073/pnas.1507228112

Provided by Stanford University Medical Center